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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
HIBBERT, CATHERINE S	

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1636	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/537,075	KEBELER ET AL.	
	Examiner	Art Unit	
	CATHERINE HIBBERT	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 January 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants Amendment to the Claims filed 15 January 2010 is received and entered. Claims 1-15 are pending and under examination.

Response to Amendment/Arguments

35 USC 103(a) Rejections

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-11 and 13-15 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Wilms et al (Biotech Bioengeer, 2001, Vol. 73, No. 2, pp. 95-103, see whole article, particularly the Abstract, pp. 97-98, 100, of record) in view of Moralejo et al (J. Bacteriol, 1993, Vol. 175, No. 17, pp. 5585-5594, see whole article, particularly Fig. 1, first full paragraph on p. 5591, of record) for reasons of record and presented herein.

The applicant's arguments have been fully considered but are unpersuasive.

The applicant's response is to traverse the rejection. Specifically, the applicant argues that the Wilms reference "is actually teaching away from using a host cell that is defective in genes other than the rhaB gene" and that accordingly, "Wilms and Moralejo are not combinable

and a *primafacie* case of obviousness has not been established". The applicants recite in a footnote the following case law regarding this point:

> It is well established that under 35 U.S.C. § 103 the Examiner must consider the reference in its entirety, *i.e.* as a whole, including portions that teach away from the claimed invention. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984); see also *KSR*, 127 S. Ct. at 1740; MPEP § 2141.03 (VI). It is improper to combine references where the references teach away from their combination. See MPEP § 2145 (X)(D)(2) (citing *In re Grasselli*, 713 F.2d 731,743,218 USPQ 769, 779 (Fed. Cir. 1983).

The applicants submit that:

> Wilms discloses a method for recombinantly expressing nucleic acid sequences using an expression system based on the rhamnose-inducible rhaBAD promoter in a rhaB defective host cell. The method taught in Wilms was characterized by the authors as being one of the most cost-effective means to enhance cell mass and protein production. See Wilms, page 101, right Col., 1st paragraph. At the time of developing their method, the gene cluster encoding the enzymes for L-rhamnose metabolism in *E. coli* was known in the art as evidenced by Moralejo. Also known in the art was the alleged suggestion made in Moralejo to block any catabolism of L-rhamnose by inactivating rhamnose isomerase. However, the authors of Wilms deliberately chose inactivating the rhaB gene of the host cell for their method. According to their own characterization, the rhaB gene was chosen for inactivation because the phosphorylation of L-rhamnulose (catalyzed by rhamnulose kinase encoded by the rhaB gene) is the first irreversible step in the degradation of L-rhamnose to dihydroxyacetone phosphate and L-lactaldehyde. Wilms, page 98, left Col., lines 4-8. As discussed in the Discussion section at pages 101-102, various factors may affect the specific productivity of a cell. Thus, any changes to an established expression system, including substituting rhaB- defective host cell with rhaA- defective host cell as suggested by the Examiner, would likely affect the specific productivity of a cell. Thus, one skilled in the art, upon reading Wilms, would not have simply modified the method taught therein by using a host cell that is defective in a different gene with a reasonable expectation of success that the productivity of the cell would be maintained.

Moreover, the applicants submit that the references are not combinable for the following additional reason:

> depending on the cultivation conditions, different concentration of inducer (i.e. L-rhamnose) is required for induction of the rhaBaD promoter in the method taught in Wilms. For instance, in shake-flask experiments, 0.1 g/L of L-rhamnose is allegedly

> sufficient for induction of the rhaBAD promoter. See Wilms at page 100, left Co1., lines 1-3 of the 2nd paragraph. In high-cell-density fermentation such as production in a fermenter, however, higher concentration of L-rhamnose is needed for effective induction of the promoter. See Wilms at page 100, left Col., 2nd paragraph, and Figure 6. As described therein and demonstrated in Figure 6, at a concentration of 0.5 g/L, the rhamnose was almost completely taken up from the cells but the enzymatic activity produced by the induction of the rhaBAD promoter was only about half of the activity obtained in shake-flask experiments. See Wilms at page 100, left Col., 2nd paragraph. It is thus clear that the concentration of 0.5 g/L of L- rhamnose was not sufficient for effective induction of the rhaBAD promoter in high-cell-density fermentation. As also described therein, a concentration of 2 g/L of L-rhamnose seems to be optimal for effective induction of the rhaBAD promoter in high-cell-density fermentation conditions. Thus, the problem to be solved in Wilms is how to achieve an effective production comparable to that obtained in shake-flask experiments in high-cell-density fermentation conditions such as production in a fermenter while uses only low concentration of inducer. Neither Wilms nor the art provides any suggestion as to how to solve this problem. Further, because the expression system using the rhaB-defective host cell taught in Wilms produces effective production in shake-flask experiments, one skilled in the art, upon reading Wilms, would have been motivated to search for any differences between the two different cultivation conditions (i.e. shake-flask and high-cell-density fermentation) and make necessary modifications accordingly in order to solve such a problem. As such, a skilled artisan would not have expected that the problem can be attributed to the use of the rhaB-defective host cell and thus, would not have been motivated to consult with the rhamnose operon described in Moralejo and substitute the rhaB-defective host cell with a host cell that is deficient in a different gene such as the rhaA gene.

In addition, the applicants cite in a footnote the following case law:

> It is well established that under 35 U.S.C. § 103 the Examiner cannot selectively pick and choose from the disclosed parameters without proper motivation as to a particular selection. The mere fact that a reference may be modified to reflect features of the claimed invention does not make the modification, and hence the claimed invention, obvious unless the prior art suggested the desirability of such modification, *In re Mills*, 916 F.2d 680, 682, 16 USPQ2d 1430 (Fed. Cir. 1990); *In re Fritch*, 23 USPQ2d 1780 (Fed. Cir. 1992) (emphasis added). "[R]ejections on obviousness cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.., a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art.., it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does." See *KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385, 1396 (2007) (emphasis added). Thus, it is impermissible to simply engage in a hindsight reconstruction of the claimed invention

where the reference itself provides no teaching as to why the applicant's combination would have been obvious. *In re Gorman*, 933 F.2d 982, 987, 18 USPQ2d 1885, 1888 (Fed. Cir. 1991).

The applicant's arguments have been fully considered but are not persuasive for reasons of record and presented herein.

Applicants currently amended claim 1 is drawn to a method for expressing nucleic acid sequences in prokaryotic host cells (such as *E. coli*) comprising: (a) introducing into a prokaryotic host cell at least one DNA construct which is capable of episomal replication in the prokaryotic host cell and comprises a nucleic acid sequence to be expressed under the transcriptional control of an L-rhamnose-inducible promoter, wherein the L-rhamnose-inducible promoter is heterologous with regard to the nucleic acid sequence, (b) selecting prokaryotic host cells which comprise the DNA construct in episomal form, and (c) inducing the expression of the nucleic acid sequence by addition of L-rhamnose to a culture of the selected prokaryotic host cells, wherein the concentration of L-rhamnose in the medium is from 0.01 g/l to 0.5 g/l, wherein the prokaryotic host cell is at least deficient with regard to L-rhamnose isomerase.

Wilms et al. teach a method for expressing nucleic acid sequences in *E. coli* wherein circular episomal plasmids (pAW178, pBW24, less than 100K in size) are used to express a heterologous polypeptide (the enzyme L-*N*-carbamoylase) wherein the sequence encoding the polypeptide is operably linked to the *E. coli* rha_{BAD} promoter which comprises at least one RhaS binding site which is a functional equivalent of SEQ ID NO:5 and expression of the heterologous polypeptide is induced by addition of L-rhamnose to the culture. Wilms et al. show induction by addition of a concentration of 0.5 g/L rhamnose (e.g. p. 100, left column, and Figure 6). The host cells have the RhaB gene inactivated and the cells are used to produce a heterologous

polypeptide enzyme, L-*N*-carbamoylase. Wilms et al. teach that inactivation of the RhaB gene was desirable because it reduced consumption of the expensive inducer L-rhamnose.

Wilms et al. does not teach inactivation of the L-rhamnose isomerase gene in the host cell.

Moralejo et al. teach the gene cluster encoding the enzymes for L-Rhamnose metabolism in *E. coli*. Moralejo et al. teach the gene encoding the rhamnose isomerase (RhaA) (functional equivalent of SEQ ID NO:9) and that inactivation of this gene would be expected to block any catabolism of L-rhamnose.

The claimed invention is essentially described by Wilms et al. The only difference involves the inactivation of the host cellular RhaA gene. Wilms et al. inactivated the host cellular RhaB gene in order to reduce the consumption of the expensive inducer L-rhamnose whereby the normal rhamnose catabolism pathway in the cell is inhibited.

The ordinary skilled artisan, seeking to develop a method for production of heterologous polypeptides in prokaryotic cells, would have been motivated to use the method disclosed by Wilms et al. and modify said method by inactivating the RhaA gene because Moralejo et al. teaches that inactivation of the RhaA gene would be expected to block any catabolism of L-rhamnose in the cell, thereby greatly reducing the amount of the expensive inducer L-rhamnose needed to induce the expression of the recombinant polypeptide.

It would have been obvious for the ordinary skilled artisan to do this because inactivation of the RhaA gene in the host cells would greatly reduce the amount of L-rhamnose needed to induce the recombinant expression of the polypeptide of interest in the cell and thereby reduce the cost of using the system exemplified by Wilms et al.

Given the teachings of the prior art and the level of skill of the ordinary skilled artisan at the time of applicants' invention, it must be considered, absent evidence to the contrary, that the ordinary skilled artisan would have had a reasonable expectation of success in practicing the claimed invention because Moralejo et al teach that rhaA mutants (isomerase deficient) were expected to block any catabolism of L-rhamnose at the time of the invention (above) and Wilms et al teach a method for expressing nucleic acid sequences encoding heterologous polypeptides in *E. coli* wherein the sequence encoding the polypeptide is operably linked to the *E. coli* rha_{BAD} promoter which comprises at least one RhaS binding site which is a functional equivalent of SEQ ID NO: 5 and where expression of the heterologous polypeptide is induced by addition of L-rhamnose to the culture. The host cells have the RhaB gene inactivated and the cells are used to produce a heterologous polypeptide enzyme.

Specifically, in response to applicant's argument that Wilms reference "is actually teaching away from using a host cell that is defective in genes other than the rhaB gene" and that accordingly, "Wilms and Moralejo are not combinable", the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981). Contrary to the applicant's assertion that the Wilms reference is teaching away from using a host cell that is defective in genes other than the rhaB gene, no where in the Wilms reference can this assertion be found in the Wilms reference. The positive teaching of a successful use of the rhaB gene mutants does not teach away from trying other host cells in

defective genes with similar function, but rather suggests to one of ordinary skill in the art that the success of the Wilms report would lead to a reasonable expectation of using other known genes which perform a similar function (i.e. as shown by Moralejo et al).

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, contrary to the applicant's assertions that there is not some teaching, suggestion, or motivation to do so, the ordinary skilled artisan, seeking to develop a method for production of heterologous polypeptides in prokaryotic cells, would have been motivated to use the method disclosed by Wilms et al. and modify said method by inactivating the RhaA gene because Moralejo et al. teaches that inactivation of the RhaA gene would be expected to block any catabolism of L-rhamnose in the cell, thereby greatly reducing the amount of the expensive inducer L-rhamnose needed to induce the expression of the recombinant polypeptide (e.g. see Wilms et al abstract).

Lastly, in response to the applicants additional reason why the references were not combinable beginning with the recitation: "depending on the cultivation conditions, different concentration of inducer (i.e. L-rhamnose) is required for induction of the rhaBaD promoter in the method taught in Wilms", this argument is not persuasive because the applicant's argument is not commensurate with the scope of the claims, as written. The base claim 1 is drawn to wherein

the concentration of L-rhamnose in the medium is from 0.01 g/l to .05 g/l and Wilms et al. show induction by addition of a concentration of 0.5 g/L rhamnose (e.g. p. 100, left column, and Figure 6).

Therefore, in view of the foregoing, the method of Claims 1-11 and 13-15, as a whole, would have been obvious to one of ordinary skill in the art at the time the invention was made. Therefore, the claims stand properly rejected under 35 USC *§103(a).*

Claim 12 stands rejected under 35 U.S.C. 103(a) as being unpatentable over Wilms et al in view of Moralejo et al as applied to Claim 1 above and further in view of Israelsen et al for reasons of record and presented herein.

The applicant's arguments have been fully considered but are unpersuasive.

The applicant's response is to traverse the rejection. The applicant argues that

> as discussed above, Wilms and Moralejo, alone or in combination, do not render the main claim obvious. Since claim 12 depends from claim 1, the cited references, Wilms and Moralejo, further in view of Israelsen, would not render claim 12 obvious for essentially the same reasons as detailed above.

The applicant's arguments have been fully considered but are unpersuasive for reasons of record and for reasons provided above as applied to the rejection of the independent Claim 1. As the independent Claim 1 stands rejected as unpatentable over Wilms in view of Moralejo, the dependent Claim 12 also stands rejected as Wilms in view of Moralejo, as applied to Claim 1, above, and further in view of Israelsen et al.

Applicants invention is as recited in the above 35 USC 103(a) rejection. In addition, applicants recite that the nucleic acid sequence encoding the recombinant protein is selected from the group consisting of chymosines, proteases, polymerasen, saccharidases,

dehydrogenases, nucleases, glucanases, glucose oxidases, a-amylases, oxidoreductases, peroxidases, laccases, xylanases, phytases, cellulases, collagenases, hemicellulases, lipases, lactases, pectinases, amyloglucosidases, glucoamylases, pullulanases, glucose isomerases, nitrilases, esterases, nitrile hydratases, amidases, oxygenases, oxynitrilases, lyases, lactonases, carboxylases, collagenases, cellulases, serum albumins, factor VII, factor VIII, factor IX, factor X, tissue plasminogen factors, protein C, von Willebrand factors, antithrombins, erythropoietins, colony-stimulating factors, cytokines, interleukins, insulins, integrins, addressins, selectins, antibodies, antibody fragments, structural proteins, collagen, fibroins, elastins, tubulins, actins, myosins, growth factors, cell-cycle proteins, vaccines, fibrinogens and thrombins.

Wilms et al. and Moralejo et al are applied as in the above 35 USC 103(a) rejection. Wilms et al and Moralejo et al do not recite the recombinant protein as being one of the members of the Markush group recited in claim 12.

Israelsen et al. (US Patent 5,837,509, see whole document, particularly column 13) recites the well known and widely practiced use of recombinant bacteria to express recombinant proteins of interest such as proteases, nucleases, lipases, etc. It is noted that the Israelsen et al reference is one among thousands of references reciting the use of recombinant bacteria to express genes of interest.

The ordinary skilled artisan, seeking to choose proteins of interest to express using the expression system disclosed by Wilms et al and Moralejo et al, would have been motivated to choose proteins such as proteases, nucleases, lipases, etc. because Israelsen et al teaches that recombinant bacteria can be used as hosts for expression of such proteins. It would have been obvious for the ordinary skilled artisan to do this because recombinant bacteria had been used for

decades to express hundreds of different proteins of interest, as exemplified by Israelsen et al. It is further noted that any of the proteins recited in claim 12, would have been obvious to the ordinary skilled artisan as recombinant bacteria had been used to express any/all of the recited proteins. Given the teachings of the prior art and the level of skill of the ordinary skilled artisan at the time of applicants' invention, it must be considered, absent evidence to the contrary, that the ordinary skilled artisan would have had a reasonable expectation of success in practicing the claimed invention.

Therefore, in view of the foregoing, the method of Claim 12, as a whole, would have been obvious to one of ordinary skill in the art at the time the invention was made. Therefore, the claim stands properly rejected under 35 USC *§103(a)*.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CATHERINE HIBBERT, whose telephone number is (571)270-3053. The examiner can normally be reached on Monday-Thursday from 8:00 AM to 5:30 PM. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/NANCY VOGEL/
Primary Examiner, Art Unit 1636

Catherine Hibbert
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